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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Application Number: 09/844,544

Filing Date: April 27, 2001

Appellant(s): ZENG ET AL.

Paul Borchardt

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/16/09 appealing from the Office action mailed 2/6/08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is substantially correct. The said statement references "the Restriction Requirement of October 2, 2002," however, the said Restriction Requirement was mailed on June 25, 2002.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

WITHDRAWN REJECTIONS

The following ground of rejections are not presented for review on appeal because they have been withdrawn by the Examiner:

- The prior rejection of record of claim 22 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

- The prior rejection of record of claims 15-26 under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), U.S. Patent No. 6,531,453 B1 (IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record), Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record) and the Merck Manual (pages 1317-1321, 16th Edition, 1992, of record).

Exclusive of said prior rejections of record, the Appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Amano *et al*. "CD1 Expression Defines Subsets of Follicular and Marginal Zone B Cells in the Spleen: β2-Microglobulin-Dependent and Independent Forms" Journal of Immunology, vol. 38 (1998), pp. 1710-1717.

Kotzin, B.L. "Systemic Lupus Erythematosus" Cell, vol. 85 (1996), pp 303-306

Zeng *et al*. "Subsets of Transgenic T Cells That Recognize CD1 Induce or Prevent Murine Lupus: Role of Cytokines" J. Exp. Med., vol. 187, no. 4 (Feb 16, 1998), pp 525-536

Blumberg *et al*. "Structure and Function of the CD1 Family of MHC-like Cell Surface Proteins" Immunol. Rev., No. 147 (1995), pp 5-29

Hughes, D. "Therapeutic antibodies make a comeback" Drug Disc. Today, vol. 3, no. 10 (1998), pp 439-442

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

(i) Claims 15-20 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record).

The Examiner notes that Inventor Samuel Strober is the senior author of both the primary reference Amano *et al* and of the secondary reference Zeng *et al* cited in the instant rejection.

Amano et al teach the conclusion "Thus, the interaction between anti-CD1 T cells and B cell expressing surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity in vivo" [systemic lupus erythematosus or SLE] (second to last paragraph of reference).

Amano *et al* teach that transgenic T cells specific for CD1 (*i.e.,* a Vβ9/Vα4.4 T cell clone, the nomenclature indicating the variable region genes encoding the T Cell Receptor, or TCR, present on the T cells that interacts with CD1) induce lupus (*i.e.,* the autoimmune disease systemic lupus erythematosis or SLE) when transferred into nude host mice that do not spontaneously develop lupus and that these nude mice develop

anti-ds DNA antibodies, proteinuria and ascites (*i.e.,* hallmarks of SLE). Additionally, the transgenic T cells activate wild-type BALB/c B cells via the cross-linking of cell surface CD1 to secrete both IgM and IgG *in vitro*. Amano *et al* teach that T cell proliferation of the CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11, indicating that the proliferation is mediated by interaction of the T cell receptor (TCR) with CD1d on the B cells.

Amano *et al* also teach that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (*i.e., mice that spontaneously develop disease*) is mediated by the $CD1^{hi}$ subset of B cells, "More recent studies have shown that the spontaneous secretion *in vitro* of both IgM and IgG by spleen cells from lupus-prone New Zealand Black/New Zealand White [*i.e.,* NZB/NZW] mice is mediated by the CD1 high subset of B cells" (*i.e., the reference teaches that spontaneous antibody secretion in the same disease model used by Applicant is mediated by CD1 positive B cells*) (especially second to last paragraph of article). Amano *et al* teach that CD1 by itself or in combination with endogenous antigens appears to be recognized by an autoreactive subset of T cells expresing the NK1.1 surface marker, and that this T cell subset has a restricted TCR repertoire that is made up predominantly of an invariant rearrangement of the $V\alpha14J\alpha281$ associated with $V\beta2$, $V\beta7$ or $V\beta8$ receptors, but that Tcells that express neither the NK1.1 marker nor the $V\alpha14$ TCR are able to recognize CD1 on syngeneic antigen presenting cells (especially column 2 on page 1710 at the first paragraph). Amano *et al* teach that CD1d is expressed in both humans and mice (first paragraph).

Amano et al do not teach the claimed method of treating systemic lupus erythematosus, including inhibiting pathogenic polyclonal B cell activation or class switching in SLE or delaying the onset of proteinuria or prolonging survival, in a human patient, said method comprising administering a CD1 blocking agent that is an antibody, including a monoclonal antibody, including wherein the monoclonal antibody is human or humanized, nor wherein the administering is by the IV route.

Kotzin teaches pathogenic IgG autoantibody production in SLE by clonal expansion of somatically mutated anti-DNA antibody-producing B cells (*i.e.,* the reference teaches *pathogenic polyclonal B cell activation in SLE (a limitation recited in instant claims 15 and 23*), a process that mimics a normal T cell dependent response to foreign antigen, involving common mechanisms of affinity maturation, and IgM to IgG *class switching* (*also a limitation recited in instant claims 15 and 23*) (especially first paragraph on page 304). Kotzin teaches that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis of SLE (especially last paragraph on page 303). Kotzin further teaches that T cells are clearly involved in the development of autoantibody production in SLE (especially column 1 on page 303 at the 2nd to the last sentence in column 1).

Zeng *et al* teach T cells with transgenic TCR that recognize CD1 of syngeneic B cells induce lupus, with resulting anti-ds DNA autoantibodies, proteinuria and immune complex glomerulonephritis, in nude mice that don't spontaneously develop lupus (especially abstract). Zeng *et al* teach anti-CD1 mAbs, including 3C11 (anti-CD1d) (especially materials and methods).

Zeng *et al* teach that severity of disease is associated with the development of the anti-ds DNA autoantibodies and with elevated serum IgG2a as has been observed with hereditary lupus, *thus indicating a correlation with hereditary disease* (especially page 534 at the second full paragraph in column 1).

Zeng et al also teach a critical correlation of cytokine secretion pattern of T cells with the amelioration versus exacerbation/induction of SLE as follows.

Zeng *et al* teach that in hereditary murine lupus, administration of IL-10 worsens the disease and administration of anti-IL-10 antibodies ameliorates the disease likely through regulation of TNF-α secretion since endogenous TNF-α is increased in lupus after the injection of the anti-IL-10 antibodies. Zeng *et al* teach that in hereditary murine lupus, administration of IFN-γ worsens lupus, and the injection of anti-IFN-γ antibodies ameliorates the disease, and that IFN-γ and IL-10 (*i.e.,* two cytokines released by Th1 cells) on one hand, and TNF- α on the other, play opposing roles in regulating the disease (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that both $CD4^+$ (*i.e.,* single positive T cells) and $CD4^-$ $CD8^-$ T (*i.e.,* double negative T cells) cells from the spleen of mice with hereditary lupus have been reported to augment the secretion of anti-ds DNA antibodies *in vitro* (especially the last sentence of the paragraph spanning columns 1 and 2 on page 533).

Zeng *et al* teach that transgenic SLE inducing cells, *i.e.,* the single positive T cells, secreted large amounts of IFN-γ and little IL-4 (*i.e.,* the single positive T cells have a Th1 phenotype), and the SLE preventive T cells, (*i.e.,* the double negative cells),

secreted large amounts of IL-4, little IFN-γ and little IL-10 (*i.e.,* the double negative cells have a Th2 phenotype) (especially page 525 first column and abstract). Zeng *et al* further teach that introduction of an IL-4 transgene (IL-4 is a Th2 cytokine) into NOD or NZW X C57BL/6 mice prevents SLE. Zeng *et al* teach "It is not surprising that T cells that secrete high levels of IFN-γ and IL-10 and low levels of IL-4 such as the transgenic anti-CD1 $CD4^+$ cells may induce or worsen lupus after activation of their CD1 receptors. One the other hand, the transgenic BM $CD4^-CD8^-$ T cells that secrete high levels of IL-4 and low levels of IFN-γ and no IL-10 would have been predicted to ameliorate disease based on their cytokine secretion pattern" (especially paragraph spanning columns 1 and 2 on page 534). *Thus, Zeng et al teach a correlation between cytokine secretion pattern of T cells with their ability to ameliorate or worsen/induce SLE, and that this correlation is not surprising.*

Zeng *et al* further teach *"The cytokine secretion pattern of the T cells plays a critical role in regulating the B cell activation even when the TCR of the T cell subsets and the CD4 and CD8 receptor expression are identical,"* thus indicating that the cytokine secretion pattern of T cells is the critical factor rather than the expression of CD4 and/or CD8 and the particular TCR on the surface of a T cell. Zeng *et al* teach "...NZB/NZW F1 mice" (*i.e., the same model of spontaneous lupus disclosed by Appellants in the instant specification*) "lose a subset of T cells..that recognizes CD1 and secretes high levels of IL-4 just before lupus develops" (*i.e., these mice lose a potective subset of T cells that secretes the Th2 cytokine IL-4 just prior to development of SLE*). "Anti-Vα14 monoclonal antibodies injected into MRL/lpr mice exacerbates the development of

lupus, and depletes this T cell subset…The latter subset shows two characteristics (recognition of CD1 and high level secretion of IL-4) with the CD4-CD8- T cell subset in the marrow that prevented lupus in this study" (*i.e.,* the reference teaches that in another model of SLE, the injection of anti-Vα14 antibodies depleted a T cell subset with Vα14 TCR phenotype that is characterized by secretion of the Th2 cytokine IL-4, said depeletion exacerbating the development of SLE) (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that "the interaction between anti-CD1 T cells and B cell expressing surface CD1 leads to the activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity in vivo." Zeng *et al* teach that an alternative pathway of T cell induced polyclonal activation of B cells and/or help for the secretion of autoantibodies to nonprotein antigens such as nucleotides*, i.e.,* the anti-ds-DNA antibodies for example, in lupus is via T cell recognition of the CD1 molecule (especially page 532 at the first paragraph of the second column).

Blumberg et al teach expression patterns of CD1 as well as antibodies to CD1. Blumberg *et al* teach that CD1c is expressed on human B cells in peripheral blood, spleen and tonsil, that CD1a, b and c are expressed on activated monocytes (GM-CSF+/- IL-4), CD1a is expressed on Langerhans cells, CD1a, b and c are expressed on dendritic cells in the dermis and CD1d is expressed in the GI tract on epithelial cells in mice and in humans as well as in other tissues at low levels, and on the majority of human B cells (especially pages 13-15). Blumberg *et al* teach antibodies to the CD1 molecules, including 3C11 (anti-CD1d) and antibodies to CD1a, b and c. Blumberg *et al* further teach that 3C11 blocks the interaction of T cells with CD1d (especially second

paragraph on page 23). Blumberg *et al* teach that 3C11 cross-reacts with human CD1d (specially page 14 at the last paragraph).

Hughes teaches administration of monoclonal blocking antibodies (such as anti-TNFα), *including humanized or human antibodies (humanized or human antibodies being a limitation recited in instant claim 18), to patients for a variety of conditions including autoimmune disease.* Hughes teaches that the conventional route to derive monoclonal antibodies has been to immunize mice, that these antibodies have widespread applications in research but can trigger immune responses because of the foreign nature of the protein when introduced into humans. Hughes teaches use of humanized or human antibodies avoids such undesirable immune responses (especially page 439).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anti-CD1d mAb taught by Zeng *et al* or Amano *et al* or the anti-CD1d antibodies taught by Blumberg *et al* to block CD1 recognition by T cells as taught by Amano *et al*, by administering them to human patients with SLE, and hence to treat pathogenic polyclonal B cell activation and/or class switching taught by Kotzin *et al*, including with humanized or human versions of the said antibodies as taught by Hughes for human patients with other autoimmune diseases, and including by the intravenous (IV) route of administration as taught for administration of T cells by Zeng *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to treat pathogenic polyclonal B cell activation and/or class

switching in a patient with SLE (*i.e.,* and to thus reduce the levels of serum IgG, including anti-ds DNA IgG and delay the onset of proteinuria and prolong survival) with a reasonable certainty of success because:

(1) Amano *et al* teach that interaction between anti-CD1 T cells and B cells that express cell surface CD1 leads to mutual activation of both cell types that results in systemic autoimmunity (SLE) *in vivo* via cross-linking of CD1 to secrete IgM and IgG, and they correlate the findings made in mice that don't spontaneously develop SLE with the observation that in hereditary SLE in NZB/NZW, the same model used by Applicant in the instant specification, spontaneous secretion of IgM and IgG antibodies by splenic B cells is mediated by CD1-expressing B cells; and

(2) Zeng *et al* teach that T cells that recognize CD1 on B cells induced lupus in nude mice with resulting production of anti-ds DNA autoantibodies, proteinuria and immune complex glomerulonephritis, as well as the observation that the cytokine profile of the T cell (of Th2 *versus* Th1 type cytokines) rather than cell surface phenotype (*i.e.,* CD4, CD8, TCR family), is critically correlated with amelioration *versus* worsening/induction of SLE in other models of SLE, including hereditary.

(3) Kotzin teaches pathogenic polyclonal B cell activation in SLE, a process that mimics a normal T cell dependent response to foreign antigen, involving common mechanisms of affinity maturation, and IgM to IgG class switching. Kotzin also teaches that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis of SLE and that T cells are clearly involved in the development of autoantibody production in SLE; and

(4) Zeng *et al* , Amano *et al* and Blumberg *et al* teach anti-CD1 mAbs, Blumberg *et al* further teach CD1 expression on various tissues and cells in the body, including B cells, and teach antibodies to CD1, including rat anti-mouse CD1d mAb 3C11 that cross-reacts with human CD1d; and

(5) Hughes teaches the administration of monoclonal blocking antibodies to patients to treat a variety of conditions including autoimmune diseases and that it is advantageous when treating human patients to use humanized rodent antibodies to avoid undesirable immune reactions to the foreign nature of the rodent antibodies.

Claim 20 is included in this rejection because the intravenous (IV) route of administration was well known in the art at the time the invention was made and Zeng *et al* teach intravenous administration of T cells. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have injected the antibody/ies via the IV route of administration.

The instant claims are included in the instant rejection because the CD1d antibodies taught by Zeng *et al* or Amano *et al* would be expected to bind to human CD1d since CD1d of mice or rat would be expected to cross-react with human CD1d due to the high degree of homology between mouse, rat and human CD1d, and as taught by Blumberg *et al* for the rat anti-mouse 3C11 antibody that cross-reacts with human CD1d.

Alternatively, the value of monoclonal antibodies that bind to a protein was well known in the art at the time the invention was made in terms of specificity, purity and yield, and Blumberg *et al* teach the human CD1d protein. A routineer would have used the same

basic technique for producing monoclonal antagonist antibodies against human CD1d protein by using an appropriate *in vitro* assay where antagonistic antibodies could be detected. Claims 24-26 are included in this rejection because the art method would be expected to treat SLE and its symptoms and to prolong survival.

(ii) Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record) as applied to claims 15-20 and 23-26 above, and further in view of the Merck Manual (pages 1317-1321, 16th Edition, 1992, of record).

The combination of Amano *et al*, Kotzin, Zeng *et al*, Blumberg *et al* and Hughes has been discussed supra, "the combined references".

The "combined references" do not teach the claimed method of treatment of SLE that further comprises administration of a second therapeutic agent for the treatment of SLE, including wherein the second therapeutic agent is an anti-inflammatory drug.

The Merck Manual teaches treatment of SLE with corticosteroid treatment (a class of anti-inflammatory drugs), such as with prednisone, in combination with immunosuppressive agents. The Merck Manual teaches that severe disease with renal damage requires immediate corticosteroid therapy in combination with

immunosuppressives, and that in both mild and severe disease, after the inflammatory response is controlled, the minimal dose of corticosteroids and other agents necessary to suppress tissue inflammation must be determined and administered, and that anticoagulant therapy is vital in patients with anti-phospholipid antibodies and recurrent thrombosis (especially first three full paragraphs on page 1320, last said full paragraph continuing on to page 1321).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered along with the immunosuppressive agent that is the blocking antibody to CD1 taught by the "combined references," an anti-inflammatory corticosteroid such as prednisone and/or the anti-coagulant taught by the Merck Manual for treatment of SLE.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more effectively treat SLE by suppressing the immune system by blocking CD1-mediated pathogenic polyclonal B cell activation or class switching as taught by the "combined references", to control the inflammatory response using corticosteroid(s) in combination with immunosuppressive agents as taught by the Merck Manual, and to treat with anti-coagulant agents in patients with anti-phospholipid antibodies and recurrent thrombosis as is taught by the Merck Manual as being vital for those patients. In addition, motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Section MPEP 2144.07.

(10) Response to Argument

(i) Claims 15-20 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record).

Appellant's arguments have been fully considered but are not persuasive.

Appellant's arguments are of record on pages 7-20 of the Appeal Brief filed 11/16/09. Appellants said arguments are largely of record in the prosecution history. However, a brief re-iteration is presented herein.

Appellant argues that that the Examiner has abstracted individual teachings from the cited references which cannot be combined to arrive at the claimed subject matter. This point will be addressed subsequent in reply to Appellant's other arguments.

In alleging that the Amano *et al* reference does not teach or suggest treatment of lupus as in the claimed subject matter, Appellant is arguing the reference separately. Appellant further argues that because Amano do not provide a reasonable expectation of success or an adequate level of predictability to administer [an] anti-CD1d antibody to treat lupus, the teachings whether alone or combined with other cited art cannot lead to the claimed invention. Such argument is, in part, arguing the reference separately. In response to Appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.1986). With regard to Appellant's allegation that Amano alone cannot lead to the claimed invention due to not providing a reasonable expectation of success or an adequate level of predictability, the Examiner will address Appellants arguments below as the points raised by Appellant apply hereto. In addition, as enunciated in the instant rejection and below in the Examiner's response to Appellant's arguments, anti-CD1d antibodies were known in the art and known to block the interaction of T cells with CD1d expressed on B cells, the ability of an antibody with a different specificity was known in the art to ameliorate systemic lupus erythematosis (*i.e.,* SLE or lupus) when administered *in vivo*, the interaction of T cells with CD1d expressed on B cells was known to result in the mutual activation of both cell types that results in hypergammaglobulinemia that characterizes SLE, and Appellant's own work in the form of the Amano *et al* and the Zeng *et al* references cited in the instant rejection (Inventor Strober is senior author of these references) teach that this interaction leads to systemic autoimmunity [SLE] *in vivo*. Thus the method steps of the instant invention were well known and well established at the time of invention, exclusive of administering the anti-CD1d antibody *in vivo*.

Appellant alleges that the Amano reference provides an *in vitro* experimental model that is an artificial system that uses one T cell line that is genetically engineered to express a receptor that recognizes CD1[d]. Appellant asserts that Amano *et al* (of which Inventor Samuel Strober is the senior author) demonstrate that this line proliferates in response to exposure to the CD1d expressed on the surface of B cells,

but in contrast, with lupus, it is the proliferation of B cells and the secretion of antibodies coupled with the later switching of antibody class that form the hallmarks of the disease. Appellant further asserts that none of these phenomena are demonstrated or even suggested by the Amano reference, and so there can be no suggestion that it is beneficial to block the interaction to prevent B cell proliferation. However, Amano *et al* teach "Thus the interaction between anti-CD1[d] T cells and B cells expressing surface CD1 leads to *a mutual activation of both cell types* [Examiner emphasis] that results in hypergammaglobulinemia and systemic autoimmunity." With regard to the issue of class switching, Appellant is arguing the reference separately. Appellant's characterization of the teachings of Amano *et al* as an *in vitro* model is also a mischaracterization. Although Amano *et al* teach that the T cell line proliferates *in vitro* in response to CD1d-transfected B cells, and B cell activation results in secretion of both IgM and IgG from CD1d B cells from lupus-prone NZB/NZW mice (*i.e.,* mice that spontaneously develop SLE and the same model used in Appellant's specification), and demonstrate blocking of said proliferation by use of an anti-CD1d monoclonal antibody, the said reference also teaches induction of SLE by the T cell line *in vivo*. With regard to the issue of "artificial system," this issue has been addressed in the prosecution history (for example in the supplemental Examiner's Answer mailed 1/12/06 on pages 3-4 and in the Examiner's Answer mailed 5/9/05 on pages 14-16).

Appellant alleges that at the time of invention, it was known that deletion of CD4+ T cells, a much larger cell population than NKT cells, effectively treats disease and knowing this fact, a person of skill would not be led to believe that lupus could be

treated by targeting a small cell population like the 3%-4% or the 0.1% in humans that NKT cells represent out of the total T cell population. Appellant alleges that instead, a person of skill would retain the commonly held belief that another, larger cell population was involved in the etiology of lupus and would not look upon the results of Amano with any expectation of success, particularly since Amano does not demonstrate that NKT cells or even T cells stimulate B cells to proliferate, secrete antibodies and later undergo class switching. However, Appellant's argument (addressed at length in the prosecution history, for example, in the Office Action mailed 1/30/07 the on pages 8-9 at items (4), (5) and (6)) ignores the teachings of Amano *et al* and Zeng *et al* that T cells do stimulate B cells to proliferate, secrete antibodies and undergo class switching, and also ignores the teaching of Amano *et al* that CD1 is recognized by an autoreactive subset of T cells expressing the NK1.1 surface marker and having a restricted TCR repertoire, but that T cells that express neither the NK1.1 marker nor the Vα14TCR are able to recognize CD1. Appellant's said argument is not evidence that a smaller subset of T cells could not be exerting the effect; 4-5% of cells in absolute numbers is 1 out of every 20 T cells in the body, and a number of activated cells can mediate an amplified response through cytokine production. Zeng *et al* correlate cytokine secretion pattern with a deleterious *versus* with a protective T cell subset in SLE.

Appellant further argues the Zeng *et al* reference, of which Inventor Samuel Strober is the senior author. Appellant argues that Zeng teaches that subsets of transplanted transgenic T cells that recognize CD1 may either induce or prevent murine lupus in recipient mice, thus allegedly explicitly outlining the unpredictability associated with T

cell involvement. Appellant alleges that further unpredictability of the references is demonstrated by the fact that as two types of T cells were created, single positive (CD4+ or CD8+) and double negative (CD4-CD8-), that injection of the double negative cells were protective of disease, while the single positive cells caused a disease phenotype, a person of skill in the art when presented with this data would be confused as the relevance of the interaction between T cells and B cells since these are two examples of T cells with the same receptor producing contradictory results in the same model. However, as enunciated in the instant rejection, Zeng *et al* clearly teach "It is not surprising that T cells that secrete high levels of IFN-γ and IL-10 and low levels of IL-4 such as the transgenic anti-CD1 CD4+ cells may induce or worsen lupus after activation of their CD1 receptors. On the other hand, the transgenic BM CD4-CD8- T cells that secrete high levels of IL-4 and low levels of IFN-γ and no IL-10 would have been predicted to ameliorate disease based on their cytokine secretion pattern…The cytokine secretion pattern of the T cells plays a critical role in regulating the B cell activation even when the TCR of the T cell subsets and the CD4 and CD8 receptor expression are identical." Thus, Zeng *et al* teach the critical correlation of cytokine production of T cells with amelioration *versus* exacerbation/induction of SLE even when cell surface phenotype in terms of CD4/CD8/TCR expression are identical, and hence indicate that T cell involvement in SLE is *not* unpredictable.

Appellant argues that Appellant has used a non-genetically engineered, hereditary model of lupus where NKT cells are present at about 3-4% of CD4+ T cell populations, has demonstrated that these CD1 reactive cells (NKT cells) are involved in mediating

lupus and that blocking CD1d ameliorates disease, delays onset in terms of proteinuria and prolongs survival. Appellant further argues that without an understanding that NKT cells mediate disease, one would simply not apprehend the disclosure of Amano and Zeng to suggest with any reasonable predictability the treatment of lupus by administration of anti-CD1d antibody. Appellant argues that in the transgenic mice, the receptor is found on all the T cells, while conversely it is only present on about 0.1% of the greater T cell population (*i.e.,* NKT cells) in humans; as such, at the time of invention, one would not reasonably extrapolate from the results seen with the universal expression of the CD1d receptor in Amano and Zeng, to the treatment of humans with an anti-CD1d antibody with any expectation of success given the exceedingly small prevalence of NKT cells in humans. However, Appellant's arguments as to the system utilized by Amano *et al* and Zeng *et al* have been addressed above and in the prosecution history; Amano *et al* do note reactivity of NK1.1 T cells with CD1d-expressing B cells, and Appellant is arguing that Appellant's own work is not obvious. Appellant's arguments directed to characterization of the mechanism of action are irrelevant, as the instant rejection establishes a reason to administer the antibody as enunciated supra. Furthermore, mouse models of lupus are intended for studying and treating human disease. Amano *et al* as well as Zeng *et al* correlate their teachings to experimental models different from Appellants as well as to the same experimental model as Applicant's, and present teachings relating to other models of hereditary murine SLE, for example, the MLR/lpr mouse model. In addition, Appellant is arguing the Kotzin, Blumberg and Hughes references separately.

Appellant alleges (at the paragraph spanning pages 12-13 of the Appeal Brief filed 11/16/09 and also referencing the Declaration of Inventor Dr. Samuel Strober filed 4/28/06 at paragraphs 4-5 of said declaration,) that because in the instant rejections the Examiner alleges that Amano and Zeng disclose T cell-B cell interaction through CD1 and Kotzin discloses involvement of B cell class switching in lupus, then it would have been obvious to treat lupus by administering anti-CD1d antibody to a human subject. This argument is a mischaracterization, as the references cited in the instant rejections teach more than what Appellant alleges; Appellant is ignoring the teachings of Amano *et al* and Zeng *et al* as a whole enunciated above in the instant rejections. Appellant further argues that the instant rejection is built on improper hindsight reasoning because at the time of invention, the prior art held the misconstrued view that CD4+ helper T cell involvement induced B cell activation or class switching. Appellant references Swain 1983 and 1984 and Wofsy and Seaman 1985 in support of this allegation. However, the Examiner has addressed this issue (for example, at items (4) and (5) on page 8 of the Office Action mailed 1/30/07). To reiterate, the Swain articles cited by Appellant demonstrate the CD4+ T cells were known in the early 1980's to interact with MHC class II molecules; however, in 1998, Zeng *et al* (cited in the instant rejections supra) recognized that a subset of CD4+ T cells are CD1-reactive and these cells secrete large amounts of IFN-γ, little IL-4, and induce lupus (SLE). The Appellant-cited Wofsy and Seaman article of 1985 teaches that reduction of circulating CD4+ T cells in NZB/NZW mice using an anti-CD4 antibody reduces autoantibody concentration, retards renal disease and prolongs life. The said article does not demonstrate which CD4+ T cells

are responsible for autoantibody production, renal disease and mortality, nor that they recognize an autoantigen associated with SLE in the context of MHC class II. Appellant further argues that none of the references [cited in the instant rejection] actually show any treatment of lupus and one would not have had any expectation of success from the combined teachings of the references. However, the instant rejection provides motivation to combine the references to achieve the claimed invention with a reasonable expectation of success for the reasons herein and of record; thus it is not required that any of the references show treatment of lupus. Once again, Appellant's arguments directed to characterization of the mechanism of action [in spontaneous SLE] are irrelevant, as the instant rejection establishes a reason to administer the antibody as enunciated supra.

Appellant alleges that there is no reason to generalize that one CD1d recognizing T cell clone that induces lupus shows or implies that all CD1d recognizing T cells will induce lupus, and that Zeng teaches that CD1d recognizing transgenic T cells can induce or suppress lupus depending on the tissue of origin and the cytokine secretion pattern. Appellant argues that there was no reason to expect at the time of the paper of Zeng that the cellular and molecular mechanisms that cause lupus induced by CD1d recognizing transgenic T cells derived from a single T cell clone are the same or similar to the mechanisms that cause spontaneous lupus in mice or humans. However, the instant claims are drawn to a method of treating SLE, not to a method of preventing SLE, and the instant rejection speaks not only to the issue of correlation of cytokine secretion by T cells, but also to the issue of cytokine milieu in terms of both blocking of

cytokines and/or loss of protective T cell subsets in the exacerbation/induction *versus* amelioration of SLE in a variety of model systems of SLE, including hereditary. In addition, Amano *et al* teach that the spontaneous secretion *in vitro* of both IgM and IgG by spleen cells from lupus-prone New Zealand Black/New Zealand White mice is mediated by CD1+ B cells, *i.e.,* the cells producing the antibodies in the same hereditary murine lupus model used by Appellants are CD1d+ B cells and T cell proliferation of CD1-restricted T cells in response to CD1-transfected B cells can be blocked by use of an anti-CD1d monoclonal antibody.

With regard to Appellant's argument that Amano *et al* did not demonstrate that a T cell clone could induce the proliferation of B cells, said argument is a mischaracterization wherein Appellant is not considering the reference as a whole, as Amano *et al* teach "Furthermore, the transgenic T cells can activate wt Balb/c B cells via the cross-linking of surface CD1 to secrete both IgM and IgG in vitro." (2^{nd} to last paragraph of reference).

Appellant again argues that there is no reason to generalize that one CD1d recognizing T cell clone that induces lupus shows or implies that all CD1d recognizing T cells will induce lupus, and again argues that the reference does not teach whether the more numerous MHC recognizing CD4+ T cells will induce lupus also. The former argument has been addressed supra. Appellant's argument as to the misconception about involvement of MHC-recognizing T cells in SLE based upon references from the mid 1980's has been addressed above as noted, and in the prosecution history as noted. In addition, once again, Zeng *et al* clearly teach that their transgenic model is an

art-recognized system for studying the interaction of B cells with T cells capable of interacting with said B cells. Zeng *et al* also teach the critical correlation of cytokine profile of T cells with the induction of or protection from SLE.

Appellant argues that Amano *et al* do not teach interaction of CD1 and NKT cells because the cell line used was engineered to express a Vα4.4Vβ9 TCR, but in contrast the NKT cells from NZB/W mice as described in the instant specification, express Vα14Jα18, and thus this is further evidence that the model of Amano and Zeng would not be predictive of success in administering anti-CD1d antibodies in treatment of SLE in humans. Appellant provides further arguments to this point (see page 15 at the second full paragraph through page 17 at the first full paragraph of the Appeal Brief filed 11/16/09) that have been addressed in the prosecution history: in brief, Amano *et al* and Zeng *et al* teach that the cell surface phenotype (*i.e.,* the TCR family type, CD4 and/or CD8 expression) is not the critical correlative factor, but the cytokine profile of the interacting T cells is, and T cells that don't express the Vα14 TCR are able to recognize CD1. Amano *et al* and Zeng *et al* recognize that their transgenic mice showed symptoms of SLE, but did not develop overt SLE due to the contribution of endogenous non-transgenic T cells that competed with the transgenic T cells (*i.e.,* the antigen-induced expression of transgenic cells is inhibited by the presence of the thymus in the adoptive hosts, thus necessitating transfer of the transgenic T cells to nude mice without a thymus). Appellant is reminded that Zeng *et al* and Amano *et al* correlate their teachings using experimental models with teachings that use the same experimental model as Appellant's, as well as with a teaching relating to hereditary murine SLE in the

same model used by Appellant and with teachings related to other models of hereditary murine SLE, for example, the MLR/lpr mouse model.

Appellant also curiously makes the allegation that the preponderance of the teachings of the Amano and Zeng [references] would be more confounding than predictive as one of ordinary skill in the art at the time of invention needed to consider the entire teachings of the cited references as a whole and not extract isolated portions. However, Appellant is not considering the teachings of Amano *et al* and Zeng *et al* as a whole, as Zeng *et al* clearly teach that their transgenic and nude mouse models are art-recognized systems for studying the interaction of CD1d expressing B cells with T cells (and in the latter model, capable of interacting with said B cells in the absence of endogenous other T cell subsets). Appellant is not considering that Zeng *et al* also teach the critical correlation of cytokine profile of T cells with the induction of or protection from SLE, such correlation superseding consideration of cell surface phenotype (*i.e.,* TCR family type, CD4, CD8 expression). Amano *et al* teach that CD1 appears to be recognized by an autoreactive subset of T cells expressing the NK1.1 surface marker and that this T cell subset has a restricted TCR repertoire that is made up predominantly, but not exclusively, of an invariant rearrangement of the Vα14Jα18 associated with Vβ2, Vβ7 or Vβ8 receptors, but that T cells that do not express the Vα14 TCR are able to recognize CD1 on syngeneic antigen presenting cells. With regard to Appellants argument that Zeng concluded the at inhibitory activity of the DN transgenic BM cells was related to the presence of the transgenes since substituting BM cells from non-transgenic Balb/c mice failed to inhibit the induction of lupus

abnormalities by the SP transgenic BM cells, Appellant is reminded that Zeng *et al* teach that their system is an art-recognized model system, and the nude mouse system is useful for studying the interaction of CD1d expressing B cells with T cells capable of interacting with said B cells in the absence of endogenous other T cells subsets, that the TCR of those T cells interact with CD1d, that the T cells produce a certain cytokine profile that is beneficial in inhibiting SLE induction by a different cell type, and that the cytokine profile, not the cell surface expression of a distinct TCR family member/CD4/CD8, is the critical correlating factor.

Appellant presents an itemized list of why one of skill would not have been motivated to combine aspects from the studies presented by Amano and Zeng together or with the other cited references (see third full paragraph on page 17 of the Appeal Brief filed 11/16/09). These arguments have been addressed above and in the prosecution history as noted. The Examiner wishes to reiterate that Appellant's item "5" has been addressed on page 4 of the Reply Brief mailed 1/12/06 and in the Examiner's Answer mailed 5/9/05 on pages 141-6). Items #1-4 and #7 have been addressed supra and in the prosecution history. Item #7 has been addressed supra and in the prosecution history. With further regard to item #7 and with regard to item #8, Zeng *et al* teach that the ability of a T cell to interact with CD1d along with the cytokine profile of the T cell are the correlative factors. With regard to item #6, Zeng *et al* characterize their result as to disease induction with transgenic SP cells thus: [administration] "induced anti-ds DNA antibodies and proteinuria in most recipients" (paragraph spanning columns 1-2 on

page 533). Furthermore, Appellant does not present evidence or argument that such result is outside the range of experimental variance.

With regard to Appellant's argument that rather than finding motivation to combine references, the person of ordinary skill in the art would espouse the conventional view that CD4+ Th cells are required for activation of B cells because CD4+ Th cells are more prevalent than NKT cells and it was known that depletion of CD4+ Th cells by anti-CD4 antibodies would ameliorate disease in hereditary murine models in a simple and direct manner. However, the former portion of Appellant's argument has been addressed above, and with regard to the latter argument, Zeng *et al* teach that an alternative pathway of T cell induced polyclonal activation of B cells and/or help for the secretion of autoantibodies to nonprotein antigens such as nucleotides, *i.e.,* the anti-ds-DNA antibodies, in lupus is via T cell recognition of the CD1 molecule.

Appellant's arguments in paragraph 1 on page 18 of the Appeal Brief filed 11/16/09 have been addressed. With regard to Appellant's argument as to new clinical data to further support the discovery that blocking CD1d TCRs with antibody reduces secretion of anti-ds-DNA antibodies, a marker for lupus, the data described are taken from an *in vitro* study. Appellant describes the study thus: Normal CD-19+ B cells do not spontaneously secrete IgM or IgA in culture, and when normal NKT cells are added, such secretion is detected. In contrast, CD-19+ B cells from a lupus patient spontaneously secretes considerable amounts of IgM, IgA and IgG, and when co-cultured with NKT cells, antibody production was increased 2-10 fold. When anti-CD1d antibody was added, anti-ds-DNA IgG production was significantly reduced. Appellant

further argues that at the time of invention, one of ordinary skill in the art recognized that presentation of a non-protein antigen such as components of DNA would necessarily be restricted by CD1, not MHC, and that the CD1 molecule is recognized by NKT cells.

However, Zeng *et al* teach, as noted in the instant rejection, that an alternative pathway of T cell induced polyclonal activation of B cells and/or help for the secretion of autoantibodies to nonprotein antigens such as nucleotides, *i.e.,* the anti-ds-DNA antibodies, in lupus is via T cell recognition of the CD1 molecule, indicating that the art at the time of invention recognized that presentation of a non-protein antigen such as components of DNA would necessarily be restricted by CD1, not MHC, and that the CD1 molecule is recognized by NKT cells.

For these reasons and the reasons of record, one of ordinary skill in the art would have had motivation to combine the references with a reasonable expectation of success based upon the teachings of the cited references.

(ii) Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record) as applied to claims 15-20 and 23-26 above, and further in view of the Merck Manual (pages 1317-1321, 16th Edition, 1992, of record).

Appellant argues that the reasons provided above, the combined teachings of the cited references do not teach or suggest the claimed subject matter of independent claim 15 from which claim 21 depends and the Merck Manual does not cure the deficiencies in the grounds of rejection as presented.

However, the Examiner's reply to Appellant's argument supra, applies herein.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this Examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Marianne DiBrino, Ph.D.

/Marianne DiBrino/

Examiner, Art Unit 1644

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